UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/934,020	08/21/2001	Sydney Brenner	55525-8055.US00	7541

22918 7590 03/21/2006

PERKINS COIE LLP
P.O. BOX 2168
MENLO PARK, CA 94026

EXAMINER	
STEELE, AMBER D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/934,020	BRENNER, SYDNEY	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *1-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner for the present application has changed. However, the Technology Center (1600) and the Art Unit (1639) have remained the same.

Status of the Claims

2. Claims 1-10 are currently pending.

Claims 7-10 are currently under consideration.

Election/Restrictions

3. Applicant's election without traverse of Group II in the reply filed on April 9, 2003 is acknowledged.

4. Claims 1-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 9, 2003.

5. Applicant's election with traverse of Sau3A as the species of first restriction endonuclease, the "M adapter" as the species of Exo III resistant linker, Taq I as the species of second restriction endonuclease, and the "Q adapter" as the species of Exo III susceptible linker in the reply filed on July 28, 2003 is acknowledged. The traversal is on the ground(s) that the "invention can be carried out using any of a large number of known restriction endonucleases" and "thousands of linkers" could be utilized. This is not found persuasive because the species are structurally and/or functionally different.

The election requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

6. The information disclosure statement filed March 11, 2003 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. A copy of the non-patent literature of Lisitsyn et al. Science. Volume 259(5097): 946-951, 1993 was not provided.

Drawings

7. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Fig. 2A (214); Fig. 2B (126), (234), and (236); Fig. 2C (254) and (260); Fig. 2D (269), (270), (271), and (272); Fig. 3 (308); Fig. 5A (556); and Fig. 8B (864). Corrected drawing sheets in compliance with 37 CFR 1.121(d), **or amendment to the specification to add the reference character(s) in the description** in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **written description** rejection.

9. With regard to the written description requirement, the attention of the Applicant is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)] (the case is referred to herein as "*Lilly*").

Additionally, it is noted that written description is legally distinct from enablement: "Although the two concepts are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures that the inventor

conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.*

Although directed to DNA compounds, this *Eli Lilly* holding would be deemed to be applicable to any compound or a generic of compounds; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the compound or generic(s). In this regard, applicant is further referred to *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997); "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001); and *Univ. Of Rochester v G. D. Searle and Co.* 249 F. Supp. 2d 216 (W.D.N.Y. 2003) affirmed by the CAFC on February 13, 2004 (03-1304) publication pending.

Additionally, *Lilly* sets forth a two part test for written description:

A description of a genus of cDNA's may be achieved by means of a recitation of: a representative number of cDNA's, defined by nucleotide sequence, falling within the scope of the genus OR of a recitation of structural features common to the members of the genus. See *Regents of the University of California v. Eli Lilly & Co.* 119 F.3d 1559 (Fed. Cir. 1997) at 1569.

Finall y, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the

inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Additionally, Cf. University of Rochester v G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation, and Pfizer Inc., No. 03-1304, 2004 WL 260813 (Fed. Cir., Feb. 13, 2004) held that:

Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

10. In the present instance, the specification discloses only limited examples that are not representative of the claimed genus of a "reference library" that is derived from the following reagents: nucleic acid fragments, a first restriction endonuclease, and a second restriction endonuclease; nor do the claims recite sufficient structural feature(s) which is(are) common to members of the genus sufficient to demonstrate possession of the genus. The instant claims define a "reference library" as a "mixture of heterogeneous nucleic acid fragments". The claimed "reference library" is only defined by functional properties (e.g. ability to be cleaved by restriction endonucleases and ability to anneal). The CAFC held that a functional definition is insufficient to adequately describe a product, therefore, an adequate written description not based on a functional definition is necessary.

The Examiner further notes the present claims stated by Applicant are broader in scope that those that were held to be impermissible in *Lilly* because, unlike *Lilly*, Applicants' claims encompass a vast number of "nucleic acid fragments" that make up a "reference library". Here, the Applicant claims a method of making a "reference library" (please refer to claims 7-10). The scope of these claims include a vast number of sequences because the specification and claims do not place any limit on the number of components (e.g. nucleic acids) or the type of components (e.g. natural or unnatural nucleic acids). Therefore, Applicant is using an inadequately described "nucleic acid fragment" derived from cleavage of inadequately described "restriction endonucleases" to inadequately describe the claimed "reference library". Consequently, there is no teaching that would allow a person of skill in the art to determine *a priori* that the Applicant was in possession of the full scope of the claimed invention at the time of filing because there is no common structural attributes that can link together all of the claimed "nucleic acid fragments" and "restriction endonucleases" that make the "reference library".

While the general knowledge and level of skill in the art for utilizing restriction endonucleases to make nucleic acid fragments is high, this knowledge and level of skill does not supplement the omitted description because specific, not general, guidance is needed for the "reference library" being made by cleaving nucleic acid(s) with restriction endonucleases. Since the disclosure fails to describe the common attributes or characteristics that identify all of the members of the genus or even a substantial portion thereof, and because the genus is vast and highly variant (e.g. billions of fragments), the limited examples in the specification (please refer to Examples 1-3 in the Specification) are insufficient to teach the entire genus.

The specification discloses only limited examples that are not representative of the claimed genus of a "reference library", "nucleic acid fragments", or "restriction endonulceases"; nor do the claims recite sufficient structural feature(s) which is(are) common to members of the genus sufficient to demonstrate possession of the genus. For example, the specification teaches "reference libraries" of p0T2S and p1T2S plasmids derived from the pUC19 plasmid (see Example 1), genomic DNA isolated from white blood cells of diabetic and nondiabetic patients (see Example 2), and pUCSE plasmids derived from the pUC19 plasmid (see Example 3). Moreover, specific restriction endonucleases were utilized to produce the above mentioned "reference libraries". If different restriction endonucleases were utilized to digest the starting material, a completely different "reference library" would be formed. Therefore, the teachings in the specification are general teachings relating without guidance as to the individual components of the product. In addition, there are numerous "nucleic acid fragments", "restriction endonucleases", and/or "reference libraries" that could be employed in the invention with little direction or guidance for one of skill in the art to practice the claimed invention. The expedient statements in the specification do not relate to an adequate disclosure or how to make and use the claimed invention. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to adequately describe the vast genus. Thus, Applicant does not appear to be in possession of the claimed genus.

11. Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

Claim 7 is drawn to a method of making a reference library comprising:

(A) digesting pooled nucleic acid with a restriction endonuclease,

(B) ligating an Exo III resistant linker to the fragment(s) of (A),

(C) digesting the product(s) of (B) with a restriction endonuclease,

(D) ligating an Exo III susceptible linker to the product(s) of (C),

(E) digesting the product of (D) with Exo III,

(F) denaturing the product of (E) and hybridizing,

(G) contacting the product(s) of (F) with a second member to enrich and form a reference population of restriction fragments.

The invention as claimed encompasses all known nucleic acid fragments and/or reference libraries and all potential nucleic acid fragments and/or reference libraries since virtually any nucleic acid can be cleaved with at least one restriction endonuclease (e.g. present claim 7). The claimed invention states that a reference library is produced via various steps of digestion with various restriction endonucleases. The claimed invention does not include any structural information regarding the nucleic acid fragments that make up the reference library except that the starting nucleic acid and subsequent fragments contains restriction site(s). Moreover, Exo III susceptible and Exo III resistant linkers are added to the nucleic acid fragments and no structural features of the linkers are provided except for the art-recognized structure that a blunt end or 5'

overhang must be present for Exo III activity and a 3' overhang for Exo III resistance. In addition, the claimed invention does not include any structural information regarding how the first or second restriction endonuclease is chosen. Are a certain number of cuts (via a restriction endonuclease) advantageous? Should only restriction endonucleases that recognize "common" sequences be utilized? Should the linker be formulated so that it is resistant to the restriction endonucleases utilized? Can the first and second restriction endonucleases be the same? Should the first restriction endonuclease cleave a "common" sequence and the second restriction endonuclease cleave a less "common" sequence or vice versa? Wouldn't "common" sequences be different in different species?

The Specification provides a "laundry list" of restriction endonucleases including Sau 3A, Taq I, Bst YI, Tsp 509I, Nla III, Msp I, Hin P1 I, Hha I, Aci I, Bsp 120I, Eco RI, Pac I, Bbs I, Bam HI, Dpn II, Pst I, Eco RV, Hind III, Bse RI, Bbv I, Xho I, Cla I, and Sap I (please refer to Figures 6-10; page 14, lines 10-19; page 35; page 37, line 12; and Examples 1-3). In addition, the specification teaches a Q, ssssN, M, ZavaW, SEQ ID No: 14, and SEQ ID No. 15 adaptors (please refer to page 51, lines 26-28; page 52, lines 1-6, page 53, lines 16-30). Additionally, the Applicant asserted that the invention as claimed encompasses "any of a large number of known restriction endonucleases" and "thousands of linkers" in the response received on July 28, 2003 (see page 2, last paragraph). Moreover, there are over 200 commercially available restriction endonucleases each of which recognizes a unique sequence (see the New England Biolabs® website, for instance) and millions of linkers that could be engineered with blunt ends, 5' overhangs, or 3' overhangs comprising dsDNA, DNA-RNA hybrids, and combination double stranded (ds) and single stranded nucleic acids. Furthermore, the specification does not teach

how the first or second restriction endonucleases should be chosen. Therefore, one skilled in the relevant art would not reasonably conclude that the Applicants had possession of the entire scope of the invention as claimed since the structural limitation of the cleavage site for the restriction endonuclease(s) is not included in the claimed invention.

12. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

With the exception of the above mentioned (see section 11, last paragraph) linkers and restriction endonulceases as disclosed by the specification, the skilled artisan cannot envision the method of claims 7-10. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. The phrase "second cleavage ends" of claim 7 (line 21, page 60) is vague and indefinite because it is unclear as to the 'lower limit' of the instant claimed "second cleavage ends". The first recitation of the "second cleavage end" recites the limitation of "a second cleavage end" (i.e. a lower limit of one) whereas the phrase "second cleavage ends" implies a lower limit of two.

16. The terms "first restriction sites" and "second restriction sites" in claim 7 are relative terms which render the claim indefinite. The terms "first restriction sites" and "second restriction sites" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Are the first restriction sites simply the initial site where the initial restriction endonuclease cleaves to produce the initial cleavage ends? Are the second restriction sites simply the subsequent sites where the subsequent restriction endonuclease cleaves to produce the subsequent cleavage ends? Are the first and second restriction sites the same or different? Can the method steps be reversed or does the first restriction sites have to be utilized in the first step in the method? Can the second restriction sites be utilized in the initial step of the method? Are first and second restriction sites utilized to indicate a preferred order? Will the method still produce the desired reference library if the order is reversed?

17. The phrase "some of which comprise a second cleavage end" in claim 7 (line 19 of page 60) is a relative phrase which renders the claim indefinite. The phrase "some of which comprise a second cleavage end" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Does "some of which comprise a second cleavage end" mean a certain number or percentage? If 5%, 10%, 20%, 40%, 60%, 80%, etc. of the restriction fragments comprise a cleavage end, is this considered "some of which comprise a second cleavage end"? If two, four, eight, sixteen, thirty-two, etc. of the restriction fragments comprise a cleavage end, is this considered "some of which comprise a second cleavage end"? Is a certain number or percentage of the restriction sites required to have a cleavage end in order for the method to produce a reference library?

18. The terms "resistant" and "susceptible" in claims 7 and 10 are relative terms which renders the claim indefinite. The terms "resistant" and "susceptible" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Since, the activity of enzymes is dependent on temperature, salt concentration, and the ratio of enzyme to product, it is not clear if the sequence is resistant or susceptible to Exo III via structural restraints (e.g. 5' overhang for susceptible and 3' overhang for resistant) or changes in temperature, salt concentration, or ratio of enzyme to product. Is the "susceptible" linker simply in excess of the "resistant" linker? Is the same linker utilized and digested under different temperatures or salt concentrations?

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

20. Claim 7 is drawn to a method of making a reference library comprising:

(A) digesting pooled nucleic acid with a restriction endonuclease,

(B) ligating an Exo III resistant linker to the fragment(s) of (A),

(C) digesting the product(s) of (B) with a restriction endonuclease,

(D) ligating an Exo III susceptible linker to the product(s) of (C),

(E) digesting the product of (D) with Exo III,

(F) denaturing the product of (E) and hybridizing,

(G) contacting the product(s) of (F) with a second member to enrich and form a reference population of restriction fragments.

21. Claim 7 is rejected under 35 U.S.C. 102(e) as being anticipated by Short et al. U.S. Patent 6,352,842 B1 (filed March 26, 1999).

Short et al. teach directed evolution utilizing restriction endonucleases and exonulcease III (please refer to the abstract). Short et al. teach methods of directed evolution including steps for digesting nucleic acids with various restriction enzymes or polynucleotide-acting enzymes and optionally repeating those steps (e.g. present claim 7 steps (A) and (C); please refer to

column 5, lines 1-15, column 9, lines 49-65, column 16, lines 36-54, column 56, lines 23-67, columns 57-58, and column 59, lines 1-6), steps for producing Exo III resistant and susceptible nucleic acids or linkers and ligation (e.g. present claim 7 steps (B) and (D); please refer to column 9, lines 66-67, column 10, lines 1-11, column 12, lines 4-16, and column 38, lines 24-67), steps for digesting nucleic acids with Exo III (e.g. present claim 7 step (E); please refer to column 37, lines 9-67, column 38, and column 39, lines 1-35), and steps for denaturing and hybridizing nucleic acids (e.g. present claim 7 step (F); please refer to column 37, lines 10-22 and 55-67, and column 38, lines 1-7). In addition, Short et al. teaches that the products of the directed evolution methods can be bound and enriched for members of the nucleic acid population which hybridize or bind (e.g. present claim 7 step (G); please refer to column 40, lines 38-60). Furthermore, Short et al. states that any commercially available or non-commercially available polynucleotide endonucleases can be utilized in the directed evolution methods including the presently elected species of Sau3A I and Taq I as evidenced by Roberts and Macelis (please refer to column 56, lines 42-57 and Roberts and Macelis, REBASE – restriction enzymes and methylases, Nucleic Acids Research, 24(1): 223-235, 1996). Therefore, one of skill in art would have anticipated the presently claimed invention in view of the teachings of Short et al.

22. Claim 7 is drawn to a method of making a reference library comprising:

(A) digesting pooled nucleic acid with a restriction endonuclease,

(B) ligating an Exo III resistant linker to the fragment(s) of (A),

(C) digesting the product(s) of (B) with a restriction endonuclease,

(D) ligating an Exo III susceptible linker to the product(s) of (C),

(E) digesting the product of (D) with Exo III,

(F) denaturing the product of (E) and hybridizing,

(G) contacting the product(s) of (F) with a second member to enrich and form a reference population of restriction fragments.

23. Claims 7-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Barany et al. U.S. patent 6,027,889 (filed May 28, 1997).

Barany et al. teach various PCR and LDR methods to form a library of nucleic acids (please refer to column 5, lines 39-50). Barany et al. teach methods including the steps of digesting genomic DNA with restriction endonucleases including Taq I (e.g. present claim 7 step (A); please refer to column 24, lines 21-54, column 40, lines 18-46, and Examples 1 and 6), adding adjustment or linker sequences and having both exonuclease resistant and susceptible sequences (e.g. present claim 7 step (B); please refer to column 26, lines 6-36, column 40, lines 18-46, and Table 11), digesting nucleic acids with Exo III (e.g. present claim 7 step (E); please refer to column 26, lines 6-36), denaturing and hybridizing various nucleic acids (e.g. present claim 7 step (F); please refer to column 32, lines 34-42 and Examples 4 and 9-10). In addition, Barany et al. teach that the method steps can be repeated (e.g. present claim 7 steps (C)-(D); please refer to Examples 4, 6, and 9-10). Furthermore, Barany et al. teach contacting to optimize for a population (e.g. present claim 7 step (G); please refer to column 36, lines 23-37). Moreover, Barany et al. teach that Exo I can be utilized (e.g. present claims 8-9; please refer to column 26,

lines 2-36). Therefore, one of skill in art would have anticipated the presently claimed invention in view of the teachings of Barany et al.

Claim Rejections - 35 USC § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. U.S. Patent 6,352,842 B1 (filed March 26, 1999) and Strathmann U.S. Patent 6,480,791 B1 (filed October 26, 1999).

Short et al. teach directed evolution utilizing restriction endonucleases and exonulcease III (please refer to the abstract). Short et al. teach methods of directed evolution including steps for digesting nucleic acids with various restriction enzymes or polynucleotide-acting enzymes (e.g. present claim 7; please refer to column 56, lines 23-67, columns 57-58, and column 59, lines 1-6), steps for producing Exo III resistant and susceptible nucleic acids or linkers (e.g. present claim 7; please refer to column 38, lines 24-67), steps for digesting nucleic acids with Exo III (e.g. present claim 7; please refer to column 37, lines 9-67, column 38, and column 39, lines 1-35), and steps for denaturing and hybridizing nucleic acids (e.g. present claim 7; please refer to column 37, lines 10-22 and 55-67, and column 38, lines 1-7). In addition, Short et al. teaches that the products of the directed evolution methods can be bound and enriched for members of the nucleic acid population which hybridize or bind (e.g. present claim 7; please refer to column 40, lines 38-60). Furthermore, Short et al. states that any commercially available

or non-commercially available polynucleotide endonucleases can be utilized in the directed evolution methods including the presently elected species of Sau3A I and Taq I as evidenced by Roberts and Macelis (please refer to column 56, lines 42-57 and Roberts and Macelis, REBASE – restriction enzymes and methylases, Nucleic Acids Research, 24(1): 223-235, 1996).

However, Short et al. does not teach Exo I or biotin attached to a linker.

Strathmann teaches various methods of nucleic acid amplification and sequencing (please refer to the Summary columns 3-4). Strathmann teaches the use of various single strand dependent nucleases including S1 nuclease and mung bean nuclease (e.g. present claim 8, please refer to column 27, lines 21-53). In addition, Strathmann teaches the use of the single-strand dependent nuclease Exo I (e.g. present claim 9; please refer to column 15, lines 20-36). Furthermore, Strathmann teaches the attachment of biotin to various nucleic acid tags (e.g. present claim 10; please refer to column 13, lines 1-14).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the methods of directed evolution taught by Short et al. with the Exo I and biotin taught by Strathmann.

One having ordinary skill in the art would have been motivated to do this because both Short et al. and Strathmann teach methods which include PCR (please refer to Methodology section columns 28-34 of Short et al. and columns 13-15 of Strathmann). In addition, Strathmann teaches that tags including biotin are utilized to distinguish different sample polynucleotides in order to identify the polynucleotides (please refer to column 4, lines 38-67, column 5, lines 1-31, column 13, lines 1-5, column 27, lines 5-20, and column 30, lines 35-47). Furthermore, Strathmann teaches that the use of Exo I or other single-strand dependent nucleases is important

for enhanced PCR amplification or to destroy mismatched duplexes and single-strand DNA (e.g. DNA without a complementary strand hybridized; please refer to column 15, lines 20-36 and column 27, lines 21-53).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the methods of directed evolution taught by Short et al. with the Exo I and biotin taught by Strathmann because of the examples provided by Strathmann (please refer to Examples 1-4) and Short et al. (please refer to Examples 1-7).

Therefore, the modification of the methods of directed evolution taught by Short et al. with the Exo I and biotin taught by Strathmann render the instant claims prima facie obvious.

26. Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. U.S. patent 6,027,889 (filed May 28, 1997) and Barany et al. U.S. Patent 6,534,293 B1 (filed January 5, 2000).

Barany et al. (6,027,889) teach various PCR and LDR methods to form a library of nucleic acids (please refer to column 5, lines 39-50). Barany et al. teach methods including the steps of digesting genomic DNA with restriction endonucleases including Taq I (e.g. present claim 7; please refer to column 24, lines 21-54, column 40, lines 18-46, and Examples 1 and 6), adding adjustment or linker sequences and having both exonuclease resistant and susceptible sequences (e.g. present claim 7; please refer to column 26, lines 6-36, column 40, lines 18-46, and Table 11), digesting nucleic acids with Exo III (e.g. present claim 7; please refer to column 26, lines 6-36), denaturing and hybridizing various nucleic acids (e.g. present claim 7; please refer to column 32, lines 34-42 and Examples 4 and 9-10). In addition, Barany et al. teach that

the method steps can be repeated (e.g. present claim 7; please refer to Examples 4, 6, and 9-10). Furthermore, Barany et al. teach that Exo I can be utilized (e.g. present claims 8-9; please refer to column 26, lines 2-36).

Barany et al. (6,027,889) does not teach biotin attached to a linker.

Barany et al. (6,534,293) teach methods for assembling genomic maps of an organism's DNA (please refer to the abstract). Barany et al. teach methods including the steps of cleaving DNA with restriction endonucleases including Taq I and adding linkers or adapters (please refer to column 11, lines 42-67, column 23, lines 7-18, column 28, lines 62-67, column 29, lines 1-20). In addition, Barany et al. teaches that the linkers can also have biotin tags (e.g. present claim 10; please refer to Tables 8-9 and 13).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the PCR and LDR methods of Barany et al. (6,027,889) with the biotin tag of Barany et al. (6,534,293).

One having ordinary skill in the art would have been motivated to do this because Barany et al. (6,534,293) teach improved PCR and LDR methods to save time and money (please refer to column 11, lines 34-39). Furthermore, Barany et al. teach that biotin labels can be utilized to minimize false positives during the PCR and LDR methods and to purify specific sequences (please refer to column 66, lines 60-67 and columns 67-68).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the PCR and LDR methods of Barany et al. (6,027,889) with the biotin tag of Barany et al. (6,534,293) because of the various examples provided by Barany et al. (please refer to Examples 1-10 of 6,027,889 and Examples 1-6 of 6,534,293).

Therefore, the modification of the PCR and LDR methods of Barany et al. (6,027,889) with the biotin tag of Barany et al. (6,534,293) render the instant claims prima facie obvious.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ADS
March 7, 2006

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600